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| | |
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| Application No. | S970346 |
| Date of filing | 14 May 1997 |
| Applicant | GALEN (CHEMICALS) LIMITED an Irish company, of Belgard Road, Tallaght, Dublin 24, Ireland. |

PRIORITY DOCUMENT

Dated this 15th day of May, 1998

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S970346

FORM NO. 1

**REQUEST FOR THE GRANT OF A PATENT**
**PATENTS ACT, 1992**

The Applicant named herein hereby request

___ the grant of a patent under Part II of the Act

_X_ the grant of a short-term patent under Part III of the Act

on the basis of the information furnished hereunder.

1. **APPLICANT**

**Name** GALEN (CHEMICALS) LIMITED

**Address** Belgard Road, Tallaght, Dublin 24, Ireland

**Description/Nationality** An Irish Company

2. **TITLE OF INVENTION**

"Topical Compositions"

3. **DECLARATION OF PRIORITY ON BASIS OF PREVIOUSLY FILED APPLICATION FOR SAME INVENTION (SECTIONS 25 & 26)**

| Previous filing date | Country in or for which filed | Filing No. |
|---|---|---|
| None | | |

4. **IDENTIFICATION OF INVENTOR(S)**

**Name of person believed by Applicant to be the inventor**

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5. **STATEMENT OF RIGHT TO BE GRANTED A PATENT (SECTION 17(2)(B)**

By virtue of a Deed of Assignment dated May 7, 1997

**Contd./...**

S970346
APPLICATION No.

PPA1048

# TOPICAL COMPOSITIONS

This invention relates to topical compositions for administration to the human or animal species. As used herein, the term 'topical' is intended to mean any accessible body surface such as, for example, the skin and mucosal epithelia such as nasal, rectal, buccal, ocular, pulmonary and rectal epithelia. The term 'topical' is also intended to embrace gastrointestinal epithelium. In particular, the invention relates to topical compositions containing a eutectic mixture of pharmacologically active agents which exhibit enhanced mutual topical absorption.

A binary eutectic mixture of phenyl salicylate-thymol is known [1], in which the pure solids have melting point ranges or melting points of 41-43°C and 51.5°C, respectively. Upon intimate admixture of the two solids, a homogeneous liquid phase is observed above the melting point of the highest melting component. Admixture of the two solids results in a mutual lowering of their melting points such that, at various compositions of the mixture and at various temperatures below the melting point of the highest melting component, pure liquid phenyl salicylate can coexist homogeneously with pure liquid thymol, pure solid thymol can coexist with pure liquid phenyl salicylate and pure solid phenyl salicylate can coexist

with pure liquid thymol. Eventually, when the temperature has been lowered sufficiently, pure solid phenyl salicylate coexists with pure solid thymol. A plot of melting point versus composition of the mixture displays a minimum point between two intersecting lines at which a homogeneous liquid phase coexists with each of the respective homogeneous solid phases. This point is known as the eutectic point or eutectic temperature. Mixtures of solids that exhibit such behaviour are known as eutectic mixtures. The eutectic point of 13°C for phenyl salicylate-thymol is observed at 34% by weight of thymol in phenyl salicylate.

Most published scientific literature concerning the formation of eutectic mixtures relates to the field of metallurgy, in particular to the formation of solders and the behaviour of alloys [2], where the formation of lower melting point eutectic mixtures is generally regarded as advantageous. By contrast, however, the formation of a eutectic mixture in the pharmaceutical or veterinary fields in which a liquid phase develops at normal storage temperatures, is usually regarded as problematic and undesirable. Thus, US Patent 5,512,300 teaches that the anti-inflammatory drug ibuprofen readily forms eutectic mixtures with each of the antihistamine drugs terfenadine, diphenhydramine and astemizole, but that formation of such

eutectic mixtures results in stability problems for ibuprofen in solid dosage forms and is, therefore, to be avoided. Indeed, US-A-5,512,300 teaches a method of preventing formation of such mixtures by amalgamation of ibuprofen and an alkali metal.

Transdermal delivery of a pharmacologically active agent (drug) conventionally requires that the drug be presented to the intact skin surface in a lipophilic form in solution in order to penetrate the lipophilic skin barrier and, whilst the mucosal epithelium is less organised at a molecular level as an absorption barrier, similar requirements apply to transepithelial drug penetration. In addition, drug levels in solution should be as close as possible to saturation, to provide the highest possible concentration gradient across the absorption barrier. A solution of a drug in a lipophilic form is achieved by including either a water miscible co-solvent or an emulsified oil phase in which the drug is first dissolved in an oil or mixture of oils as solvent. However, both of these measures reduce the thermodynamic driving force of the drug in the carrier and, therefore, hinder drug penetration, by providing a competing phase for drug migration, but the negative effect of the latter measure is more pronounced. To overcome this, higher drug loadings are required. In addition, the use of co-

solvents such as ethanol or propylene glycol are known to cause adverse local reactions on the skin and epithelia.

A consequence of the perceived pharmaceutical formulation problems caused by formation of eutectic mixtures is that there has been only one commercial application of a pharmaceutically useful composition containing a eutectic mixture, specifically, a binary mixture of local anaesthetic agents, which is disclosed in EP-B-2425. Since this disclosure which was published in 1979, there have been no further commercial developments in this area.

EP-B-2425 teaches that mixture of a specified weight ratio of two local anaesthetics, preferably lidocaine and prilocaine, each in free base form results in the formation of a eutectic mixture as an oil with a melting point below 40°C. The teaching is limited to the formation of a eutectic mixture from two local anaesthetically active agents. In this connection, it will be appreciated that all compounds with local anaesthetic activity possess a common structural pattern, in which a substituted aromatic hydrophobic component is linked via an amide, ester, ketone or ether group to an intermediate alkyl chain terminating in a hydrophilic moiety [3]. There is no suggestion that the invention has

applicability beyond eutectic mixtures of two local anaesthetic agents. Furthermore, there is no suggestion that pharmaceutically useful eutectic mixtures can be formed from anything other than structurally similar active agents.

Surprisingly, it has now been found that pharmaceutically useful eutectic mixtures can be formed between at least two pharmacologically active agents, which may be structurally and/or pharmacologically diverse agents, such that their mutually enhanced topical penetration can be achieved. Preferred eutectic mixtures are those in which the agents possess complementary but different pharmacological activities.

The present invention surprisingly overcomes the problems referred to hereinbefore, which hinder topical drug absorption, by providing a eutectic mixture comprising at least two pharmacologically active agents in their lipophilic (substantially water-insoluble) form, the eutectic mixture being dispersed in, but not substantially dissolved in, a hydrophilic, pharmaceutically acceptable carrier. Preferably, such carrier should contain no co-solvent or additional oil phase.

Accordingly, it is a novel aspect of the invention to provide a topical composition comprising a binary eutectic mixture of first and second pharmacologically active agents in a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C. Preferably, the first pharmacologically active agent has a melting point between 35 and 75°C, preferably 40-50°C, and the second pharmacologically active agent has a melting point between 40 and 150°C, preferably between 40 and 90°C, with the proviso that the first agent is not prilocaine or tetracaine when the second agent is selected from benzocaine, lidocaine, bupivacaine, mepivacaine, etidocaine or tetracaine.

Alternatively, the topical composition comprises a ternary eutectic mixture of the first and second pharmacologically active agents and a third pharmaceutically acceptable component, in the pharmaceutically acceptable carrier. Preferably, the third pharmaceutically acceptable component should have a melting point between 40 and 150°C, preferably between 40 and 75°C. More preferably, the third component comprises a third pharmacologically active agent.

As used herein, the term 'pharmacological agent' means any agent used in the prophylaxis or therapy of any

condition affecting the health of the human or animal species. Exemplary agents useful in the invention include, but are not limited to, antimicrobial agents such as mupirocin, triclosan, chlorocresol, chlorbutol, iodine, clindamycin and econazole, anti-inflammatory analgesic compounds such as ibuprofen and ketoprofen, opioid analgesics such as fentanyl, rubefacients such as methyl nicotinate, anti-motion sickness agents such as scopolamine, antispasmodic agents such as oxybutynin, anti-worm agents such as levamisole, as well as vitamins, minerals and other nutrients.

As used herein, the term 'pharmacologically acceptable component' means any agent not intended for use in the prophylaxis or therapy of any condition affecting the health of the human or animal species and includes, but is not limited to, lauric acid, stearyl alcohol, menthol and thymol.

Said pharmaceutically acceptable carrier should be suitable for administration of the eutectic mixture and should not adversely interfere with the formation and stability of said mixture, and should be suitable for topical application. Exemplars of topical compositions include gels, lotions, suspensions, creams, aerosol sprays, transdermal patches, medicated dressings and soft

gelatin capsules for rapid gastrointestinal absorption. Preferably, the pharmaceutical carrier of use in the invention should be substantially hydrophilic in that said carrier should contain only water as the solvent and there should be no lipophilic phase present, other than that formed by the eutectic mixtures of the invention. Most preferably, the pharmaceutically acceptable carrier should contain one or more gelling or suspension agents known in the art. Exemplars of such gelling or suspension agents include carbomers, modified cellulose derivatives, naturally-occurring, synthetic or semi-synthetic gums such as xanthan gum, acacia and tragacanth, modified starches, co-polymers such as that formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylate derivatives sold under the trade name Eudragit™.

Advantageously, the pharmaceutically acceptable carrier should include one or more surfactants (emulsifying agents) compatible with any pharmacologically active agents or pharmaceutically acceptable components present. Non-ionic, cationic and anionic surfactants are suitable. Non-ionic surfactants, for example, Tweens and Spans (Trade Marks) are preferred.

The topical compositions of the invention may be prepared by incorporating the binary or ternary eutectic

mixtures into the pharmaceutically acceptable carrier such that the oil phase components of the eutectic mixture are homogeneously distributed throughout the carrier and such that said homogeneity is maintained over normal storage periods at ambient temperature. Homogeneous distribution of the binary or ternary eutectic mixtures may be achieved by any suitable method known in the art, such as the formation of oil-in-water gelled emulsions.

It is a second aspect of the present invention to provide a binary eutectic mixture comprising first and second pharmacologically active agents, in which the first agent has a melting point between 35 and 55°C, preferably 40-50°C, and the second agent has a melting point between 40 and 150°C, preferably between 40 and 90°C, the eutectic mixture having a melting point of less than 40°C, with the provisos that the first agent is not prilocaine or tetracaine when the second agent is selected from benzocaine, lidocaine, bupivacaine, mepivacaine, etidocaine or tetracaine; that the first agent is not ibuprofen when the second agent is selected from terfenadine, diphenhydramine hydrochloride or astemizole; and that the first and second agents do not comprise S and R enantiomers of ibuprofen, ketoprofen, etodolac or propranolol.

It is a third aspect of the present invention to provide a ternary eutectic mixture of first and second pharmacologically active agents with a third pharmaceutically acceptable component, in which the first agent has a melting point between 35 and 55°C, preferably 40-50°C, the second agent has a melting point between 40 and 150°C, preferably between 40 and 90°C, and the third pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C, the eutectic mixture having a melting point of less than 40°C. Preferably, the third component comprises a third pharmacologically active agent, with the proviso that the first, second and third agents are not lower alkyl esters of p-hydroxybenzoic acid.

The invention will now be exemplified by reference to the following.

**Example 1**

| | |
|---|---|
| Ibuprofen | 5.00 g |
| Methyl nicotinate | 5.00 g |
| Hydroxyethylcellulose (Natrosol™ 250 HHX) | 3.00 g |
| Nipastat™ sodium | 0.20 g |
| Citric acid monchydrate | 1.03 g |

| | |
|---|---|
| Disodium phosphate dodecahydrate | 3.65 g |
| Tween 80 | 0.50 g |
| Water | 81.62g |

A topical composition in the form of an emulsified gel preparation suitable for treating musculo-skeletal disorders is prepared by using a binary eutectic mixture of ibuprofen, an anti-inflammatory analgesic agent and methyl nicotinate, a rubefacient. To the required weight of water in vessel 1 is added, sequentially and with constant stirring, the required weights of citric acid monohydrate, disodium phosphate dodecahydrate and Nipastat™ sodium. In vessel 2, the required weights of ibuprofen and methyl nicotinate are mixed together until the mixture liquifies, and the required weight of Tween 80 is then added with stirring. The contents of vessel 1 are then added to the contents of vessel 2, slowly and with stirring. Finally, the required weight of hydroxyethylcellulose is added slowly and with constant stirring.

Figure 1 is a phase diagram for the ibuprofen-methyl nicotinate system. It was prepared by determining the melting points, using differential scanning calorimetry, of systems containing from 0 to 100% by weight of methyl nicotinate in ibuprofen. Figure 1 indicates the phases

(solid or liquid) present at various temperatures and compositions of the mixture. Thus, it can be seen that the two pharmacologically active agents form a liquid eutectic mixture at compositions between 20-68% w/w of ibuprofen in methyl nicotinate, at a temperature of 20°C. The eutectic point occurs at a temperature of -20°C for a composition of 50% w/w ibuprofen in methyl nicotinate.

The enhanced penetration of both ibuprofen and methyl nicotinate through a representative barrier membrane, polydimethylsiloxane sheeting (Silescol™, thickness 0.0625 mm), is shown in Figure 2 for ibuprofen and in Figure 3 for methyl nicotinate. It is known in the art that polydimethylsiloxane is a good model lipophilic barrier for transdermal and transepithelial Fickian diffusion studies and is often used in formulation development work as an alternative to human or animal skin [4]. Thus, the penetration of ibuprofen and methyl nicotinate across a Silescol™ barrier from a formulation prepared according to the example quoted hereinbefore (Formulation A) was determined using a Franz finite dose diffusion apparatus [5]. The cell contained 12 ml of phosphate-buffered saline, pH7 as the receiving fluid and 1 g of the formulation was applied evenly across the surface of the barrier membrane at the start of the experiment. The receiving fluid in the reservoir was completely replaced

with fresh fluid at five minute intervals from the start of the experiment, thus ensuring sink conditions throughout, with the concentration of the active pharmacological agent in each five minute sample being determined by reverse-phase high performance liquid chromatography. Figures 2 and 3 express the respective results obtained as the cumulative amount of each pharmacological agent penetrating the membrane from Formulation A over a 30 minute period.

Similarly, the cumulative penetration of each pharmacologically active agent was determined for a formulation (Formulation B) in which the emulsifying agent - Tween 80 - was omitted, all other aspects of the formulation being identical to Formulation A, the results obtained again being shown in Figure 2 for ibuprofen and in Figure 3 for methyl nicotinate. It will be apparent to those skilled in the art that Formulation A contains a eutectic mixture of the oily active ingredients as the internal phase of a gelled emulsion whereas Formulation B is a physical mixture of the two pharmacologically active agents in a non-emulsified gel carrier, the eutectic mixture not being maintained in this case upon dilution with the aqueous component in the absence of the stabilising emulsifier. This comparison compensates for possible competition for fractional area of the barrier

membrane available for each of the simultaneously penetrating drugs. Thus, when the penetration rates across the barrier membrane of the two pharmacologically active agents are compared as between Formulations A and B, it is readily apparent from Figures 2 and 3 that significantly greater rates of penetration for both agents are achieved with the topical composition of the present invention. Indeed, the rate of penetration of ibuprofen observed with the eutectic formulation (A) is almost double that of the non-eutectic formulation (B). In order to eliminate any possible direct effect of the emulsifier (Tween 80) upon the rate of penetration of the pharmacologically active agents, the experiment described hereinbefore was repeated for Formulation C (identical to Formulation A but with the omission of methyl nicotinate) and Formulation D (identical to Formulation A but with the omission of ibuprofen). Formulations C and D gave rates of penetration for ibuprofen and methyl nicotinate, respectively, almost identical to those obtained with Formulation B (see Figures 2 and 3, respectively).

The invention is not limited to the embodiment described and exemplified herein, which may be modified or varied without departing from the scope of the invention.

## REFERENCES CITED

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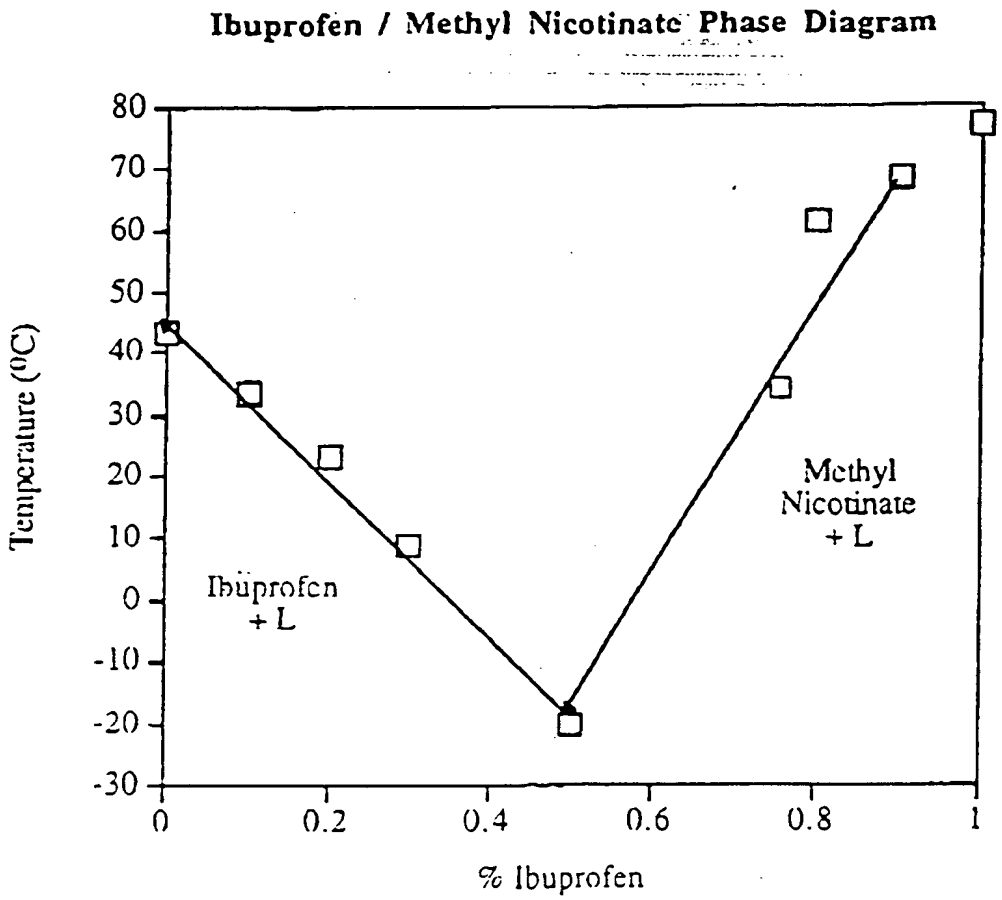

Ibuprofen / Methyl Nicotinate Phase Diagram
Temperature (°C)
80
70
60
50
40
30
20
10
0
-10
-20
-30
0
0.2
0.4
0.6
0.8
1
% Ibuprofen
Ibuprofen + L
Methyl Nicotinate + L

Figure 1

Figure 2

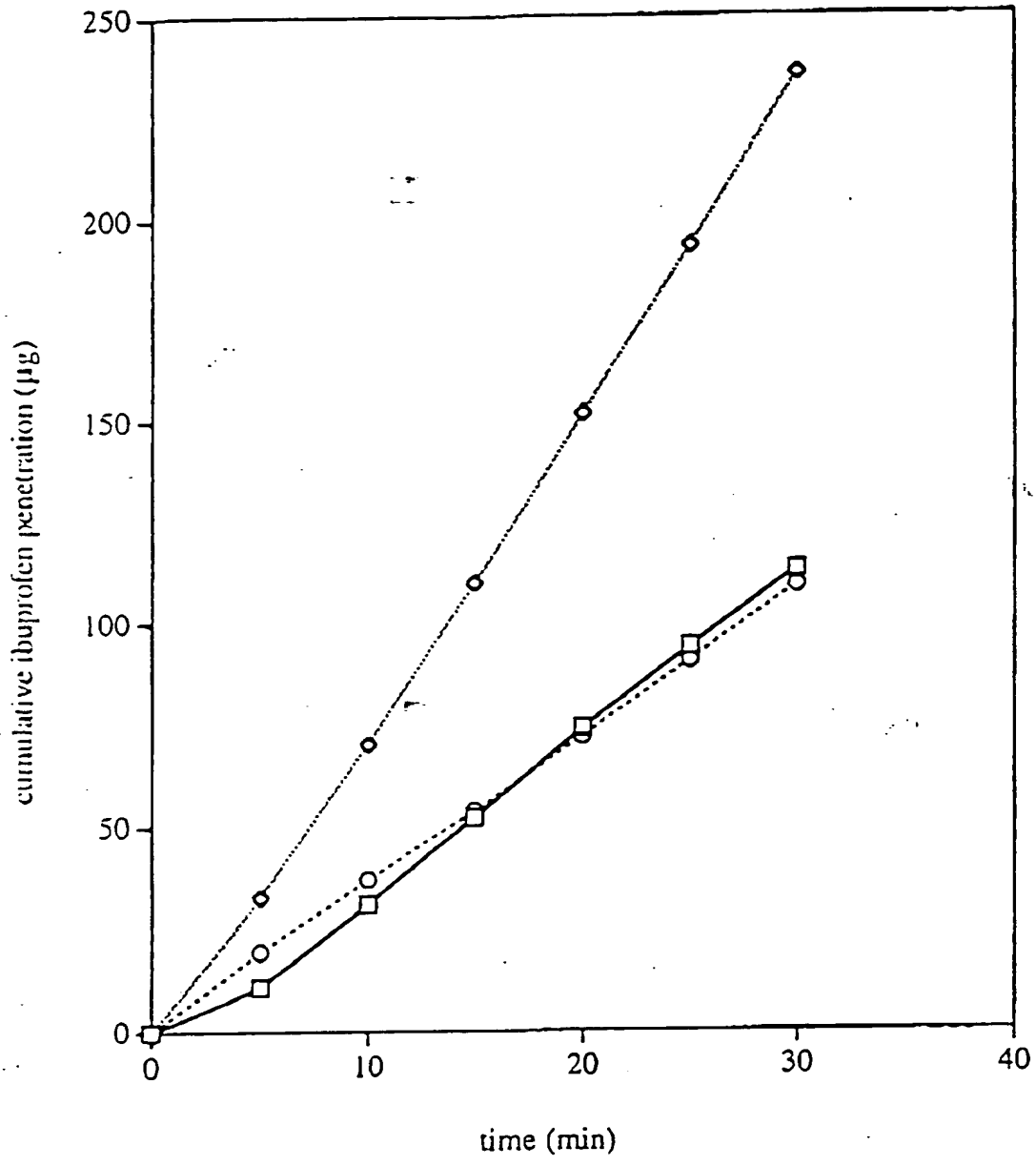
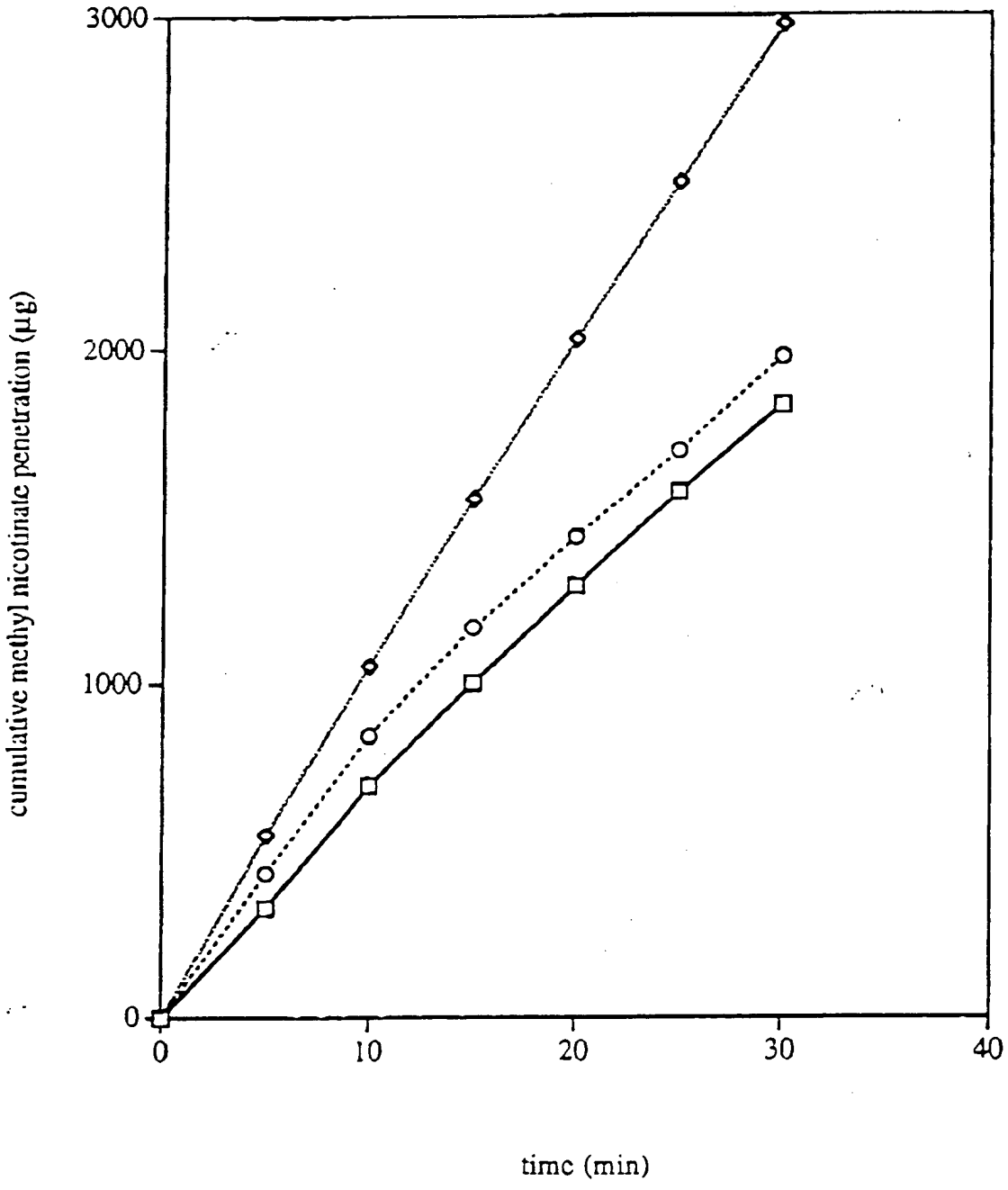

250
200
150
100
50
0
cumulative ibuprofen penetration (µg)
0
10
20
30
40
time (min)
ibuprofen penetration, formulation A
ibuprofen penetration, formulation B
ibuprofen penetration, formulation C

Figure 3


3000
2000
1000
0
cumulative methyl nicotinate penetration (µg)
0
10
20
30
40
time (min)
methyl nicotinate penetration, formulation B
methyl nicotinate penetration, formulation A
methyl nicotinate penetration, formulation D